

Oxprenolol vs Propranolol: A Randomized, Double-Blind, Multiclinic Trial in Hypertensive Patients Taking Hydrochlorothiazide

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SUMMARY Oxprenolol (O) or propranolol (P) was randomly added double-blind to the regimen of 260 patients with mild and moderate hypertension who had not responded to hydrochlorothiazide (H) alone. Both beta-adrenergic blocking agents were titrated over a range of 120 to 360 mg per day while H was continued. After 6 months of treatment, reduction of diastolic blood pressure (DBP) to below 90 mm Hg and at least 5 mm Hg less than the initial DBP was achieved in 50% of patients receiving P+H and 27% of patients taking O+H ($p < 0.001$). P+H lowered BP an additional 10.5/9.8 mm Hg compared with 6.8/7.0 mm Hg for O+H ($p < 0.02$). Reduction in heart rate was less after O+H (average, 8.4/min) than after P+H (average, 12.3/min, $p < 0.01$). The number of dropouts, morbid events, and reported side effects between the two regimens was not significantly different except that more patients complained of impotence with P+H than with O+H ($p < 0.05$). (Hypertension 3: 250-256, 1981)

KEY WORDS • beta adrenergic blockers • controlled therapeutic trial • cooperative study • antihypertensive drugs

USE of beta-adrenergic blocking agents in the treatment of hypertension has increased rapidly since the introduction of propranolol 15 years ago. Propranolol, a nonselective beta-adrenergic blocking agent without intrinsic sympathomimetic activity, was the first of these agents to be widely used clinically. Consequently, it is often used as a reference standard for comparison with other beta-adrenergic blocking drugs.^{1,2} Differences in pharmacology, hemodynamics, antihypertensive effects, and side effects make it important to carry out controlled trials comparing the various beta-adrenergic blocking drugs to assess clinically relevant differences.

Oxprenolol (Trasicor) is a highly specific, but nonselective, beta-adrenergic blocking agent with membrane-stabilizing properties similar to those of

propranolol. Unlike propranolol, however, it also has intrinsic sympathomimetic activity (ISA).³⁻⁷ Oxprenolol has beta-adrenergic blocking activity comparable to propranolol⁸ but its negative inotropic effect is less pronounced.^{6,7,9} This latter property of oxprenolol should lessen the risk of heart failure or excessive bradycardia as compared with the administration of propranolol or cardioselective blocking agents such as metoprolol or atenolol.

This study was designed to compare the efficacy of oxprenolol and propranolol in the treatment of patients with hypertension, defined as a diastolic blood pressure (DBP) of 95 through 114 mm Hg, whose blood pressure (BP) was not adequately lowered with the administration of hydrochlorothiazide alone.

Methods

Male veterans between the ages of 21 and 64 years, whose DBP was in the range of 95 to 114 mm Hg, were recruited primarily in the admitting room and outpatient clinics, and less frequently among hospitalized patients. Patients with severe complicated hypertension, serious systemic disease, and those with preexisting conditions that would interdict the use of the drug regimens, were excluded from the study. Atrial fibrillation was an exclusion factor because accurate determination of BP would be impossible. A list of the exclusions is presented in Appendix A.

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Prior therapy was discontinued for at least 4 weeks before the patients entered the trial. The nature of the study was explained to them, and their written informed consent was obtained. The study was approved by the Human Use Committee at each hospital and conformed to the principles of the Helsinki declaration. A history was then taken and a physical examination performed. Chest roentgenogram (if not taken in the previous 3 months), ECG, complete blood cell count, urinalysis, and determinations of fasting serum glucose, potassium, uric acid, cholesterol, triglycerides, and creatinine were obtained. In addition, antinuclear antibody, SGOT, and alkaline phosphatase levels were determined as indices for drug toxicity. Slit lamp examination, skin surveillance, and fluorescent antinuclear antibody tests (FANA) were performed prior to randomization and at 3-month intervals. A checklist of the known side effects associated with the administered drugs was reviewed with the patient at each visit.

The BP readings were taken in the right arm by means of a standard mercury sphygmomanometer three times in the sitting position at each clinic visit. The DBPs reported represent the average of the three fifth-phase Korotkoff readings taken with the patient in the sitting position. Pulse rate was recorded at each clinic visit.

Placebo Period

The pretreatment BP and the compliance of the patient were determined during the prerandomization period. Following a drug washout period of 4 weeks, if patients were on prior therapy they were given a bottle containing placebo, identical in appearance to the drugs used in the active drug period. They were instructed to take one capsule three times daily and to return the bottle with the remaining medication to the clinic on each visit. Patients were included in the trial if their average DBP on two successive clinic visits was in the range of 95 to 114 mm Hg provided they had taken 90% or more of the prescribed medications. A maximum of four biweekly visits were allowed to fulfill these requirements.

Hydrochlorothiazide (HCTZ) Period and Postrandomization Period

Patients meeting the placebo trial period criteria were placed on HCTZ 25 mg three times daily, and the placebo was continued. Each patient was seen biweekly for two clinic visits and, if the average DBP was less than 90 mm Hg, was dropped from the study. However, if after 4 weeks of therapy with HCTZ the average DBP was greater than 89 mm Hg, propranolol or oxprenolol was randomly assigned in a double-blind manner 40 mg three times daily while the HCTZ was continued. Doses of the beta-adrenergic blocking agents were titrated at biweekly intervals to the peak dose of 120 mg three times daily or until goal BP was achieved. The latter was defined as a DBP less than 90 mm Hg and at least 5 mm Hg below the

prerandomization level. After reaching the peak dose level, patients whose DBP exceeded 104 mm Hg during two clinic visits 2 weeks apart were removed from the trial. Other reasons for termination of participation included the development of symptomatic hypotension, serious side effects of the blocking agents, development of systemic diseases, or serious complications of hypertension (Appendix B).

Results

Prerandomization Losses

Of the 418 patients entering the study, 105 patients (25.1%) were dropped during the placebo phase. Of these, 49 were dismissed because of lack of compliance, 40 due to a BP outside the acceptable range, and 16 due to miscellaneous causes.

HCTZ was administered to 313 of the 418 patients entering the pretrial placebo period. During this HCTZ phase, 53 patients were dropped: 39 because the DBP fell to below 90 mm Hg, seven for failing to return to the clinic, two because the DBP was greater than 114 mm Hg, and five for miscellaneous reasons.

Comparability of Randomized Groups

Oxprenolol or propranolol was randomly assigned double-blind to 260 patients qualifying for randomization. Of this number, 211 patients completed 6 months of treatment. The characteristics of the patients randomly assigned to oxprenolol or propranolol were nearly identical in all respects examined (table 1). More blacks than whites were lost during the prerandomization period. The primary reason for more white patients advancing to the HCTZ phase was that more blacks demonstrated noncompliance; 26 blacks but only two whites failed to return to clinic. Eleven blacks and seven whites had BPs too low to be included in the study, while 14 blacks and eight whites were excluded because of a DBP greater than 114 mm Hg. There were no significant differences between the regimens in either the dropout rates or in the causes for the 49 dropouts that occurred in the postrandomization phase (table 2).

Changes in Blood Pressure

A major objective of the study was to compare the percent of patients on each regimen who achieved goal BPs after 1, 3, and 6 months of therapy. The values used for 1 and 3 months are the average DBPs recorded on the particular monthly visit, whereas the value at 6 months represents the average of the determinations taken at both 5 and 6 months. Fifty-three patients taking propranolol achieved goal BP pressure at 1 month, 59 at 3 months, and 54 at 6 months. Forty-four patients taking oxprenolol achieved goal BP at 1 month, 29 at 3 months, and 28 at 6 months (table 3). The differences between the regimens in the percentage of patients at goal BP was significant ($p < 0.001$) at 3 and 6 months.

TABLE 1. *Characteristics of Patients Entering and Completing Study*

	Entering	Placed on HCTZ	Randomized		Completing Study	
			Propranolol	Oxprenolol	Propranolol	Oxprenolol
No. of Patients	418	313	130	130	107	104
Age, yrs	50.3 ± 0.4†	50.8 ± 0.4	50.0 ± 0.7	51.2 ± 0.7	50.9 ± 0.7	51.2 ± 0.8
Race						
White	188 (45%)	159 (51%)	71 (55%)	68 (52%)	59 (55%)	58 (55%)
Black	229 (55%)	153 (49%)	59 (45%)	61 (47%)	48 (45%)	45 (44%)
Other	1 (0%)	1 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Weight, kg	86.5 ± 0.7	86.2 ± 0.8	87.7 ± 1.2	85.2 ± 1.3	86.4 ± 1.3	85.0 ± 1.5
Blood pressure, mm Hg						
Systolic:						
Pretreatment	150.7	150.5	149.3	150.3	149.4	150.6
Post HCTZ					137.9	137.9
Reduction					11.5*	12.7*
Diastolic:						
Pretreatment	104.0	103.9	104.1	104.2	104.0	104.1
Post HCTZ					99.5	99.2
Reduction					4.5*	4.9*
Heart rate, beats/min	78.2 ± 0.5	77.9 ± 0.6	77.8 ± 0.9	78.4 ± 1.1	77.4 ± 0.9	77.3 ± 1.3
Serum potassium, mEq/liter	4.25 ± 0.2	4.24 ± 0.2	4.21 ± .04	4.25 ± .04	4.22 ± .04	4.23 ± .05
Creatinine, mg/100 ml	1.17 ± 0.1	1.17 ± 0.1	1.18 ± .02	1.16 ± .02	1.18 ± .02	1.16 ± .02
Uric acid, mg/100 ml	6.73 ± 0.7	6.71 ± 0.7	6.73 ± .11	6.73 ± .11	6.72 ± .12	6.68 ± .10

*Using paired *t* test; *t* > 3.291, *p* < 0.001.

†Mean ± standard error number. HCTZ = hydrochlorothiazide.

The mean BP levels before and after treatment are shown in table 4. The mean reduction of SBP and DBP associated with the administration of propranolol at 1 month was 9.8/9.0 mm Hg, at 3 months 10.8/10.4 mm Hg, and at 6 months, 10.5/9.8 mm Hg. For those taking oxprenolol, the mean reductions were 7.6/7.9 mm Hg at 1 month, 7.3/7.3 mm Hg at 3 months, and 6.8/7.0 mm Hg at 6 months. The

mean reductions were significantly different between propranolol and oxprenolol at 3 and 6 months for both DBP (*p* < 0.001) and SBP (*p* < 0.05).

Pulse Rate, Body Weight, and Blood Chemistries

Pulse rate declined in both groups but significantly more in the propranolol group (table 5), the mean decrease being 12.4/min following propranolol as compared to 8.4/min after oxprenolol (*p* < 0.01). At 6 months, three patients receiving propranolol as compared to none on oxprenolol exhibited a pulse rate of 50/min or lower. No patient exhibited bradycardia of this degree prior to randomization.

Body weight increased significantly in both groups, but the mean increases were less than 1.5 kg. There was no significant difference in the degree of weight gain between the propranolol and oxprenolol groups.

Serum creatinine and uric acid levels revealed similar but insignificant changes before and after treatment with both regimens. Although serum potassium concentration increased significantly in both treatment groups (*p* < 0.01), the magnitude was small and there was no significant difference between the oxprenolol and the propranolol patients.

Side Effects

Subjective side effects not present prior to randomization but which were volunteered or elicited after randomization were varied and numerous (table

TABLE 2. *Losses Following Randomization*

Cause	Regimen	
	Propranolol	Oxprenolol
Improper entry or noncompliance:		
Noncompliance	12	9
Improperly randomized	3	3
Miscellaneous	3	6
Clinical events:		
Pulmonary emboli and death	1	0
Congestive heart failure	1	0
Diabetes-insulin dependent	0	2
Prior brain infarct with recurrent symptoms	0	1
Persistent BP > 104 mm Hg	1	2
Side effects:		
Depression	2	2
Photosensitivity due to HCTZ	0	1
Total	23	26

HCTZ = hydrochlorothiazide.

TABLE 3. *Percent of Patients Attaining Diastolic Blood Pressures Averaging Below 90 mm Hg and at Least 5 mm Hg Less than Initial Pressure*

Treatment	1 Month		3 Months		6 Months	
	No.	%	No.	%	No.	%
Propranolol	53	50%	59	55%*	54	50%*
Oxprenolol	44	43%	29	28%	28	27%

*Chi-square > 10.83; $p < 0.001$.

6). Impotence was the only significant side effect noted between regimens, in 24% of the propranolol-treated patients as compared to 14% of those receiving oxprenolol ($p < 0.05$). Wheezing and peptic ulcer symptoms were additional side effects that were more frequently encountered with propranolol than with oxprenolol, although the difference did not reach the level of significance. However, this could have occurred by chance in view of the large number of different side effects reported (table 6). There were no significant differences noted between groups with respect to other side effects. Weakness, lethargy, orthostatic dizziness, itching of the eyes, and dyspnea were the most frequent complaints. Several of these occurred in the same patient in many instances.

In view of the oculomucocutaneous syndrome reported with practolol,¹⁰ 209 patients underwent slit lamp examinations at specified intervals. There was no evidence in any of the patients either by this examination, by physical examination, or by the FANA test of the presence of this syndrome.

 TABLE 4. *Mean Systolic and Diastolic Blood Pressures Before Treatment and at 1, 3 and 6 Months after Treatment*

Blood pressure, mm/Hg	Propranolol	Oxprenolol
At randomization	137.9/99.5	137.9/99.2
At 1 month	128.1/90.5	130.3/91.3
At 3 months	127.1/89.1	130.6/91.9
At 6 months*	127.4/89.7	131.1/92.2
Mean reduction at 6 months	-10.5/-9.8	-6.8/-7.0

*Average of BP for 5th and 6th month.

Discussion

Results of the present study are presented for the patients completing the trial rather than for all patients randomized. We believe this analysis is more meaningful than to include the dropouts, and seems justified for the following reasons. First, the number of dropouts after randomization was relatively small and was approximately equal in the two treatment groups, being 23 of 130 patients or 17% of those randomized to propranolol and 26 of 130 or 20% of those randomized to oxprenolol. Second, as can be seen in table 2, the reasons for termination of the trial were not significantly different between therapeutic regimens. In particular, excessive BP was an uncommon cause for termination in both groups of patients. The most frequent reason was noncompliance, usually failure to return to clinic, which occurred nearly equally in the two groups. It would seem very unlikely, therefore, that the observed differences in antihypertensive effectiveness between oxprenolol and

 TABLE 5. *Mean Changes and Standard Errors in Pulse Rate, Body Weight, Serum K, Creatinine, and Uric Acid at 6 Months*

	Propranolol	Oxprenolol	Difference between drugs
Pulse rate (beats/min)			
At randomization	79.8 ± 0.9	79.3 ± 1.2	0.5 ± 1.6
At 6 months	67.4 ± 1.0	70.9 ± 1.0	-3.5 ± 1.4*
Change	-12.4 ± 1.0‡	-8.4 ± 1.1‡	-4.0 ± 1.5‡
Weight (kg)			
At randomization	85.4 ± 1.3	83.7 ± 1.4	1.7 ± 1.7
At 6 months	86.8 ± 1.3	84.8 ± 1.5	2.0 ± 2.0
Change	+1.4 ± 0.3‡	+1.1 ± 0.3‡	0.3 ± 0.4
Serum potassium (mEq/liter)			
At randomization	3.71 ± 0.04	3.58 ± 0.05	0.13 ± 0.06*
At 6 months	3.85 ± 0.05	3.77 ± 0.05	0.08 ± 0.07
Change	+0.14 ± 0.05*	+0.19 ± 0.06†	-0.05 ± 0.08
Serum creatinine (mg/100 ml)			
At randomization	1.22 ± 0.02	1.21 ± 0.02	0.01 ± 0.03
At 6 months	1.23 ± 0.02	1.20 ± 0.02	0.03 ± 0.03
Change	+0.01 ± 0.02	-0.01 ± 0.02	0.02 ± 0.03
Uric acid (mg/100 ml)			
At randomization	8.04 ± 0.16	7.97 ± 0.18	0.07 ± 0.24
At 6 months	8.03 ± 0.14	8.07 ± 0.16	0.04 ± 0.21
Change	-0.01 ± 0.18	+0.10 ± 0.14	-0.11 ± 0.23

Paired t test used within each regimen and two sample t test for differences between regimens.

* $t > 1.96$; $p < 0.05$.

† $t > 2.576$; $p < 0.01$.

‡ $t > 3.291$; $p < 0.001$.

TABLE 6. *New Side Effects (Volunteered and Elicited) after Randomization for 211 Patients Completing the Study*

Side effect	Propranolol patients		Oxprenolol patients	
	No.	%	No.	%
Lethargy	19	18	21	20
Depression	5	5	5	5
Nightmares	8	8	11	11
Edema	4	4	3	3
Syncope	2	2	2	2
Vertigo	13	12	13	13
Weakness	23	22	27	26
Wheezing	8	8	3	3
Dyspnea	19	18	15	14
Angina	10	9	10	10
Palpitations	12	11	9	9
Ulcer Symptoms	11	10	6	6
Anorexia	8	8	3	3
Impotence	26	24	14	14*
PND	5	5	3	3
Skin Rash	10	9	16	15
Postural Dizziness	21	20	17	16
Claudication	4	4	6	6
Itching Eyes	20	19	14	14
Other	52	49	56	54

*chi-square > 3.84; $p < 0.05$.

propranolol could be due to bias introduced by omitting the patients who were terminated from the study.

Propranolol was significantly more effective in lowering BP than oxprenolol after the third month of treatment. Not only did a higher percentage of patients receiving propranolol achieve goal BP at 6 months than those taking oxprenolol (50% versus 27%) but they also showed a greater reduction in the mean SBP and DBP ($-10.5/9.8$ mm Hg vs $-6.8/7.0$ mm Hg). While this difference is not great, it should be noted that the present study was not designed to test the effectiveness of oxprenolol and propranolol in lowering mean BP. Rather, the major objective was to determine what percentage of patients would achieve a goal level of BP. After the goal level was reached, there was no further increase in dose. Hence, the lowest tolerable levels of BP probably were not attained. The setting of a therapeutic goal below 90 mm Hg also seems to be in keeping with standard clinical practice, as most clinicians appear to use this goal in treating their patients.

Of the 54 patients receiving propranolol who achieved goal BP at 6 months, 27 also were at goal BP at 1 and 3 months. Only 15 patients receiving oxprenolol achieved goal BP at all of these clinic visits. Seventy-nine patients taking propranolol as compared to 53 patients receiving oxprenolol achieved goal BP either at 1, 3, or 6 months during the course of the

study. The percentage of propranolol-treated patients who achieved goal BP remained relatively constant from the first to the sixth month of treatment. However, the percent responders to oxprenolol fell sharply after the first month. In the oxprenolol-treated group, the percentage of patients achieving goal BP dropped from 43% at 1 month, to 28% at 3 months, to 27% at 6 months. It is not clear why the oxprenolol-treated patients exhibited a smaller percentage of responders after the first posttreatment month.

Various sources of bias were examined as possible causes for the difference in response between the two treatment groups. With respect to the severity of the hypertension, the mean SBP and DBP were nearly identical for the two groups, that is, 137.9/99.5 mm Hg for propranolol and 137.9/99.2 mm Hg for oxprenolol. In addition to the similarity of the means, the BP distribution also was not significantly different (table 7). Furthermore, the response of the patients to HCTZ was similar, the reduction averaging 11.5/4.5 mm Hg for patients later assigned to propranolol and 12.7/4.9 mm Hg for those randomized to oxprenolol. There also were no significant differences with respect to age, race, heart rate, and serum creatinine between the two groups.

The lesser response to oxprenolol is not explained by a failure to titrate the dosage of the drug appropriately. Indeed, the dosages after 6 months were considerably higher with oxprenolol than with propranolol. At 6 months, the oxprenolol dosage had been titrated to the allowed maximum of 360 mg daily in 65 of the 76 patients who had not reached goal BP as compared to 39 of 53 similar patients receiving propranolol. The principal reason for failure to titrate all of these patients to the maximum with either drug was noncompliance. At 3 months, the proportion of patients receiving the maximal dose of oxprenolol was 55% as compared to 37% in the propranolol group; at 6 months, the proportion was 73% and 53% respectively. Thus, dosages were titrated to the maximum allowed in a significantly higher percentage of patients receiving oxprenolol than in those receiving propranolol ($p < 0.01$).

The presence of 19% dropouts during the trial could represent a source of bias. While such a possibility cannot be entirely ruled out, it seems unlikely for the following reasons: first, the number of dropouts in each group were nearly the same, 22 for propranolol vs 26 for oxprenolol. Second, the various reasons for the losses, including noncompliance, morbid events, increased BP and side effects, were distributed essentially equally between the two regimens. Also, the incidence of nonterminating side effects were comparable in the two treatment groups.

It seems unlikely, therefore, that bias caused by dropouts, dissimilar groups of patients, initial responsiveness to diuretics, distribution of initial BPs, inappropriate titration of dosages, or incidence of side effects could account for the lesser antihypertensive response to oxprenolol.

Another possible explanation for the lesser antihypertensive effect of oxprenolol is that its intrinsic

TABLE 7. *Prerandomization Diastolic Blood Pressures (DBP) by Therapeutic Regimen for 211 Patients Completing the Study*

DBP (mm Hg)	No. of Patients Per Regimen	
	Propranolol	Oxprenolol
90 - 94	28	29
95 - 99	28	24
100 - 104	27	33
> 104	24	18
chi square = 1.74, ns.		

sympathomimetic activity may have antagonized the depressor effect of the beta-adrenergic blockade. Supporting this possibility was the observation that the pulse rates of patients taking oxprenolol were greater than in the patients receiving propranolol. A pressor effect has been reported in occasional patients following large doses of pindolol,⁸ which is another beta-adrenergic blocking drug with ISA properties.¹¹ However, no conclusions can be drawn from the present data concerning this question because the study was not designed to test for ISA specifically.

The results of the present trial are at variance with those previously reported. Andersson et al.¹² compared the reduction in BP obtained with the administration of oxprenolol vs propranolol in a small group of patients and concluded that the two drugs had significant and approximately equal antihypertensive activity. A similar conclusion was reached by Materson et al.¹³ after randomly assigning the beta blockers to a group of 24 patients who had not responded to HCTZ. However, their data does show a 4 mm Hg greater DBP decrease in favor of propranolol ($p < 0.05$ supine, $p < 0.025$ standing). Patients in these two studies were treated for only 8 weeks in contrast to 6 months in the current study. Gavras et al.¹⁴ randomly allocated one of the two beta-adrenergic blocking agents to 20 patients whose BP had not responded adequately to HCTZ. Treatment with 180 to 480 mg daily of the blocking agents and the diuretic was continued for 7 months. Both drugs reduced SBP and DBP similarly, propranolol by $-12/11$ and oxprenolol by $-24/15$ mm Hg.

Because of its ISA, oxprenolol may have certain advantages over propranolol such as less tendency to bronchoconstriction and less interference with myocardial contractility. With respect to the contractility, systolic time intervals recorded during the present study are being analyzed by methods previously described¹⁵ and will be reported in a later communication. In addition, Gavras et al.¹⁴ found greater suppression of the diuretic-induced increase in plasma renin activity with oxprenolol than with propranolol. Nevertheless, despite these various observations, it may be concluded from the present trial that in a significantly higher percentage of men with mild hypertension propranolol controlled the BP more effectively than oxprenolol.

Acknowledgments

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Appendix A

Exclusion Criteria

Complications of Hypertensive State

History or findings of grade III or IV hypertensive neuroretinopathy
Cerebral hemorrhage
Hypertensive encephalopathy
Dissecting aneurysm of the aorta.

Surgically Curable Hypertension

Serum Creatinine Greater than 2 mg/dl

Collagen Vascular Disease (with the exception of rheumatoid arthritis)

Conditions Interdicting Use of Proposed Drugs

History of depression
Duodenal ulcer
Greater than 1st degree heart block
Asthma

Obstructive lung disease with cor pulmonale or asthmatic wheezes

Symptomatic and objective peripheral arterial insufficiency or a history of Raynaud's phenomenon or disease

Diabetes requiring treatment other than diet

Active liver disease including cirrhosis

Psoriasis, keratitis, positive antinuclear antibody test on two successive determinations

Chronic ophthalmologically proven conjunctivitis.

Patient Unreliable

Unwilling or unable to participate.

Appendix B

Criteria for Termination

Blood Pressure Outside Protocol Range

Hypotensive Symptoms with BP less than 90 mm Hg with minimal allowed dose of test drug

Failure to Take Protocol Medications for 3 Consecutive Weeks

Possible Deleterious Pharmacological Effects of Beta Blockers

Bronchial asthma
Congestive heart failure
Peripheral vascular insufficiency (or Raynaud's phenomenon)
Depression confirmed by a psychiatrist
Gastrointestinal bleeding or peptic ulcer
Arthralgia, dermatitis or symptoms suggesting lupus erythematosus
Ophthalmological complaints not explained by ophthalmologist on any basis other than patient's drug therapy.

Major Cardiovascular Complications of Hypertension or Atherosclerosis

Central nervous system
Heart
Aorta
Kidneys.